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EXAMINER	ART UNIT	PAPER NUMBER
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DATE MAILED:
1803
02/26/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11/26/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892. 1 page
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 15 pages
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1 – 19 are pending in the applica
   Of the above, claims 3-5 and 14 are withdrawn from considerat
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-2 and 6-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these draw are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been receive ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The preliminary amendment and the election filed 2/21/90 and 11/26/91 respectively are acknowledged. Claims 1-19 are now pending in the application of which claims 3-5 and 14 are withdrawn as non-elected claims.

Applicant's election with traverse of Species V, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the subject matter of the restricted claims are all related and therefore are not independent. The suppression of autoimmune disease by oral administration routes, for any autoimmune disease, would be found in the same body of literature. There would most certainly be cross citation to similar experimentation in this field. Therefore, Applicants submit that although there may be numerous species encompassed in the claims, that an undue burden of search would not be placed on the Examiner. This is not found persuasive because Applicants attention is directed to the various autoimmune diseases encompassed in the instant invention. These are different products and the guidelines for restriction clearly support the restriction of different products (ie. the various autoimmune diseases cited in claim 2). Further, products or different groups are related or similar is not sufficient basis to assume non-restrictable subject matter because similarities or relations are not the test for distinction; independence and distinctness are the test for restriction.

Furthermore, it is apparent on its face that the various autoimmune diseases cited in claim 2 differ in function and utility from the elected autoimmune disease (ie. Multiple Sclerosis).

Contrary to Applicants assertion, the search for the various autoimmune diseases claimed would require undue burden for the reasons stated above and it is necessary to do further search in the scientific literatures inorder to conduct a complete and

thorough search for the salient features of the present invention.

With regard to Applicants allegation that they are entitled to claim additional species in the event that a generic claim thereto is found to be allowable in accordance with 37 C.F.R. 1.141(a) is not found to be persuasive because the claims are not restricted to species per se, rather, they are elected as election of species requirement described in MPEP 803.02 (Markush group) and 8.09.02 (d)(burdensome search necessary).

The requirement is still deemed to be proper and is therefore made **FINAL.**

35 U.S.C. § 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

Claims 1-2 and 6-18 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility; and the invention as disclosed is inoperative and therefore lacks utility.

Applicants claims are directed to a method of treating a T cell-mediated or T cell-dependent autoimmune diseases in animals including humans by oral or enteral administration in particular Multiple Sclerosis in which the autoantigen is myelin basic protein (MBP) or analog of MBP comprising 1-37 amino acids. Applicants teachings do not adequately explain the evidence of utility as claimed because there is no teaching in the disclosure to support the method of treating multiple sclerosis for claims 2 and 13.

There are some experimental data on certain autoimmune diseases on rats to demonstrate the effect of treatment of autoimmune diseases by oral administration. However, the murine

model does not support claims 1 and 8-10 which encompasses animals, including humans (See page 6, paragraph 2, in the specification).

Considering the nature of the treatment of autoimmune diseases such as multiple sclerosis and the limited success achieved; one skilled in the art would not accept the instantly claimed invention as obviously valid and correct without demonstration of clinical evidence for the following reasons:

In view of the broad diversity of autoimmune diseases in animals and humans, in view of the fact that animals and humans are outbred, in view of the lack of disclosure of suitable animal models for autoimmune diseases, in view of the recognized problems in the art regarding effective tolerization and in view of the lack of any evidence that tolerization would actually prevent the autoimmune diseases corresponding to the tolerizing antigen; a reasonable doubt exists as to the utility and operability of the claimed method for treating the multiple sclerosis disease claimed. Further, there is no evidence which shows that one can extrapolate the results of treating one autoimmune disease to the treatment of another, nor is there any teaching of the specific autoantigen that would be associated with the particular autoimmune disease claimed.

Furthermore, the method for treating autoimmune diseases, particularly, multiple sclerosis in animals and humans is fraught with unpredictability and uncertainty as claimed in claims 1 and 8-10. It is clear that a given autoantigen must induce an immunoprotective response against a particular autoimmune disease in a host that is susceptible to said autoantigen and must not cause adverse side effects in the host. Thus, in the absence of appropriate testing, one having ordinary skill in the art would not have reasonable expectation that the treatment against autoimmune diseases in general and in particular multiple sclerosis would be effective and induce an immunoprotective response against subsequent administration of autoantigens as

broadly claimed in the instant invention and induce such a response without any harmful side effects generally in animals and particularly in humans.

Moreover, in view of the contemporary knowledge in the art related to autoimmune diseases that all attempts to treat autoimmune diseases in humans have been unsuccessful and there is no practical therapeutic treatment for autoimmune diseases as of to date. Hence, one of ordinary skill in this art would not accept the characterization of any and all prophylactic or therapeutic treatment protocols, as believable on their face. Further, in view of the fact as of to date, the cause of multiple sclerosis in particular is not yet clearly known and in view of the fact that the obstacles to method of treatment and therapeutic approaches with regard to autoimmune diseases in humans are well documented in the literatures. The contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any autoimmune disease immunization treatment or any therapeutic regimen on its face.

Furthermore, in view of the fact there is lack of disclosure of suitable animal models and no reasonable experiments for multiple sclerosis and since Applicants invention is directed to a method of treating of autoimmune diseases in general and in particular multiple sclerosis per se in animals and humans; the data must generally be clinical, however, adequate animal data would be acceptable in those instances wherein one of ordinary skill in the art would accept the correlation to human utility. Thus, in order to rely on animal data there must exist an art recognized animal model for treating purposes (See IN re Hartop, 311 F. 2d 249, 135 USPQ 419(CCPA) 1962).

Accordingly, Applicants have to provide objective factual evidence showing the claimed method of treating multiple sclerosis would work by using accepted animal models to mimic the various autoantigens claimed generally in animals and particularly in humans and allow evaluation of active immune

response is suggested.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and use the claimed invention, i.e. failing to provide an enabling disclosure.

The disclosure is insufficient to support for a method of treating T cell-mediated or T cell-dependent autoimmune diseases in animals including humans by oral or enteral administration in particular multiple sclerosis in which the autoantigen is MBP or an analog of MBP comprising 1-37 amino acids for the reasons discussed supra.

Claims 1-2 and 6-18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-2 and 6-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite and confusing in the recitation "animal autoantigens", "fragments" and "or analogs" because these terms encompasses the whole class of autoantigens expressed by various autoimmune diseases. It is suggested that the specificity of the antigen to be identified in the generic claim. Claims 1, 15-16 and 19 are indefinite and vague in the recitation

"biologically active fragments" because this term does not specify the nature of the biological activity. Claim 2 is indefinite in the recitation of various autoimmune diseases. Amendment of the claim to limit to elected autoimmune disease (ie. multiple sclerosis) would obviate this rejection. Claims 15-19 are also indefinite in the recitation "MBP". Use of full terminology is suggested.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.**

6-13 and 15-18

Claims 1-2 and 6-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Campbell et al in view of Whitacre et al and/or further in view of Nagler-Anderson et al.

Campbell et al teach the administration of myelin basic protein parenterally in multiple sclerosis patients. The reference also suggests the use of synthetic peptide fragments (See abstract). Campbell et al differ from claims 1-2 and 6-18 in teaching the treatment of multiple sclerosis by parenteral administration of the MBP. However, Whitacre et al disclose the oral administration of MBP to protect the development of

experimental allergic encephalomyelitis (EAE). The reference suggests that oral administration of MBP may be of value in establishing a therapeutic protocols for multiple sclerosis (MS). Further, Nagler-Anderson et al teach that intragastric administration of an autoantigen (soluble II collagen) suppress on experimental autoimmune disease such as collagen -induced arthritis in mice (See abstract).

In view of the combined teachings of the prior art and in view of Applicants acknowledgments at page 8 in the specification that EAE is a model disease for MS; it would appear prima facie obvious and within the skill of the art administering autoantigens orally or enterally to protect autoimmune disease against MS. Also, the selection of appropriate dosage and autoantigens is within the skill of the art to which this invention pertains.

Further, it would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Campbell et al in view of Whitacre et al and/or further in view of Nagler-Anderson et al, thus achieving the invention as a whole for the expected benefits of treating an autoimmune disease and in particular MS and the delivery of MBP to T cells in autoimmune disease of interest by oral or enteral administration of autoantigens.

Therefore, one of ordinary skill in the art would have been motivated to combine the teachings of Campbell et al in view of Whitacre et al and/or further in view of Nagler-Anderson et al.

Accordingly, claims 1-2 and 6-18 are prima facie obvious over the prior art, absent of sufficient objective factual evidence or unexpected results to the contrary.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless--

(b) the invention was patented or described in a printed publication in this country or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Eylar.

Eylar teaches the derivisation of peptides from MBP or their analogs from various species in which the peptides are used to induce EAE in several species. As claim 19 is broadly directed to a polypeptide comprising amino acids 1-37 of MBP, a biologically active fragment thereof, or an analog thereof; the prior art anticipates or renders obvious the polypeptide composition of MBP or its analog as claimed. Although, the reference does not teach amino acids 1-37 of MBP, the claimed peptides are within the scope of the generic teachings of the reference (See Table I). Furthermore, the choice of certain polypeptide within the reference's generic disclosure is an obvious modification of the reference's teachings, absent of sufficient objective factual evidence or unexpected results to the contrary.

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1803.

Papers relating to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November

15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A Mohamed whose telephone number is (703) 308-3966.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM Mohamed/AAM
February 24, 1992

JOHNNIE R. BROWN
SUPERVISORY PATENT EXAMINER
ART UNIT 183